Hypertension

Renal denervation: latest trial shows technique is ineffective

Professor of Molecular Pharmacology **Eoin O'Brien** on new research which shows no significant reduction of systolic blood pressure in patients with resistant hypertension six months after renal-artery denervation

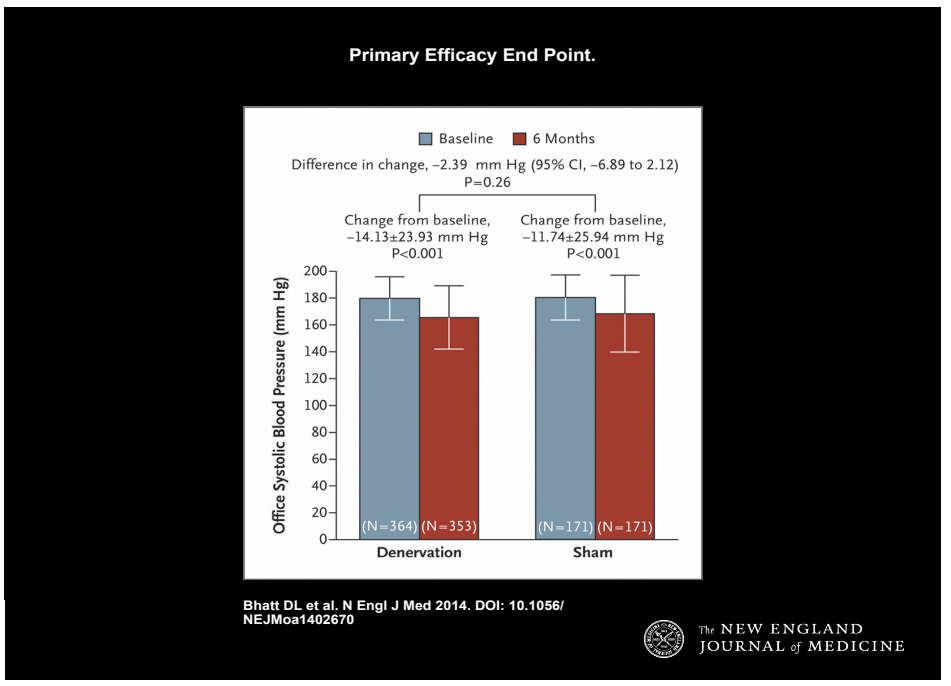

Figure 1. Primary Efficacy End Point. A significant change from baseline to six months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5mmHg. The I bars indicate standard deviations.

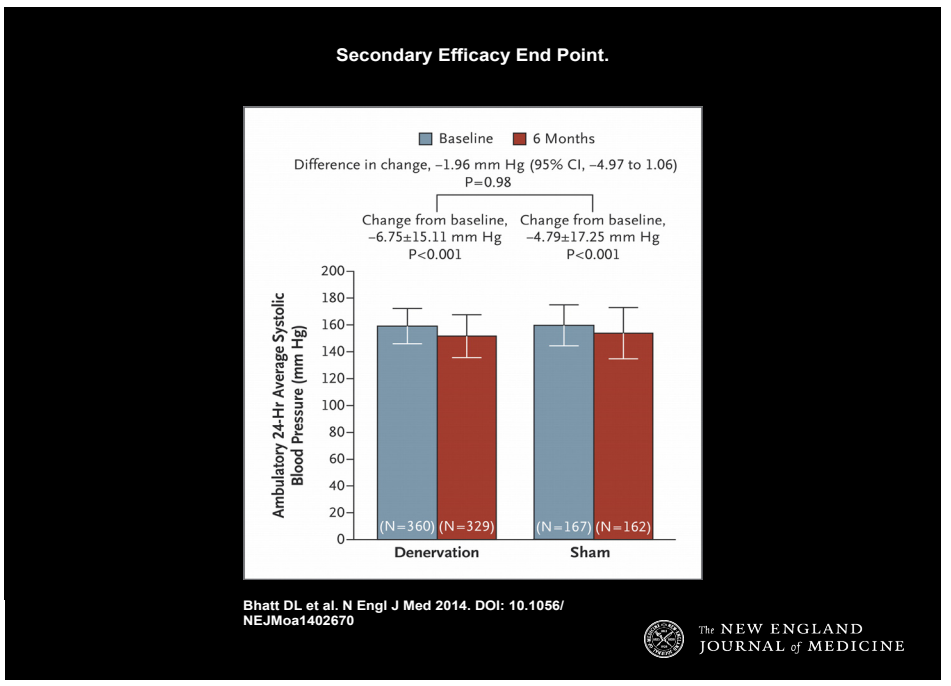

Figure 2. Secondary Efficacy End Point. A significant change from baseline to six months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2mmHg. The I bars indicate standard deviations.

I have written twice before in *Irish Medical Times* on the technique of renal sympathetic denervation that promised so much for patients with hypertension. First, in March 2012, while acknowledging that "percutaneous renal sympathetic denervation is undoubtedly a most promising cardiovascular intervention", I cautioned that "we are far from being able to make any definitive conclusions".

Then in January this year, I highlighted the press release from Medtronic – the company that had sponsored three Symplicity trials – which warned that the technique had been shown to be ineffective in the biggest and best of these trials – the Symplicity HTN-3 trial.

The results of the Symplicity HTN-1 and HTN-2 studies gave what were hailed by many as results so promising that the technique could be applied not only to patients with resistant hypertension, but also even to those with moderate blood pressure elevation.

Renal denervation would not just cure hypertension, it would also improve cardiovascular outcome in other co-morbid conditions such as heart failure, diabetes mellitus, sleep apnoea, and arrhythmias. It was anticipated that studies would soon show that the procedure would allow patients to throw away their tablets and be permanently cured of hypertension.

But there were those who questioned the impetus for a treatment that was based on economic rather than scientific considerations. Meanwhile, the headlong rush to invest vast amounts of money in an unproven procedure continued. Guidelines were drawn up for the procedure and largely ignored. Importantly, the guidelines stipulated that before resistant hypertension could be diagnosed, white-coat hypertension had to be excluded using ambulatory blood pressure monitoring (ABPM).

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This very logical stipulation was conveniently overlooked by the investigators of most trials, including Symplicity HTN-1 and HTN-2 trials, who chose office rather than ABPM as the primary endpoint. Indeed when data from ABPM were available they were seldom reported and, when analysed, did not show significant blood pressure reduction. Cautious scientists also warned that the procedure, although apparently safe in the short term, might induce changes in the future due to the more general effects of renal sympathetic denervation and possibly vascular damage to the renal arteries. Nonetheless, renal denervation moved on at an alarming pace with approval being granted in several European countries, but not in the US.

Scientific facts

Then on January 9, 2014, Medtronic issued a press release, stating that its trial on renal denervation for treatment-resistant hypertension, Symplicity HTN-3, had failed to meet its primary efficacy endpoint, which was a reduction of 10mmHg in systolic blood pressure. This study, which had commenced in September 2011, randomised 535 treatment-resistant hypertension (office systolic blood pressure > 160mmHg) to intervention with renal denervation and continuance of baseline anti-hypertensive medications, or to a control non-intervention group, who underwent renal angiography alone and were similarly maintained on baseline anti-hypertensive medications.

The Council on High Blood Pressure of the Irish Heart Foundation adopted the recommendation of the British Hypertension Society, the British Cardiovascular Intervention Society, the British Society for Interventional Radiology, the National Institute for Clinical Outcomes Research, the British Cardiovascular Society, and the Renal Association that there should be a temporary moratorium on renal denervation procedures for all patients with hypertension as part of routine care in Ireland until the data from Symplicity HTN-3 had been analysed.

The full results of this study have just been published in the *New England Journal of Medicine* (www.nejm.org, March 29, 2014DOI: 10.1056/NEJMoa1402670). They show, as anticipated, that the mean change in systolic blood pressure at six months was −14.1mmHg in the denervation group as compared with −11.7mmHg in the sham-procedure group and the change in 24-hour ambulatory systolic blood pressure was −6.7mmHg in the denervation group compared to −4.7mmHg in the sham-procedure group. All in all, statistically insignificant changes.

The conclusion was simply that "this blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension six months after renal-artery denervation as compared with a sham control". A "Dear physician" letter from Medtronic confirmed this message, and concluded that "while the primary endpoint result of the trial is not what we anticipated, we thank you for your ongoing support of the Medtronic Renal Denervation program".

Presumably all bodies associated with providing guidance to practising practitioners, specialists and patients will now endorse the earlier recommendation for a temporary moratorium, and recommend that the procedure should no longer be performed in patients with hypertension.

Lessons for the future

The major lesson to be learned from what could be called the "renal denervation debacle" is that the results of Symplicity HTN-3 were predictable and carefully conducted trials using ABPM rather than conventional blood pressure measurement could have saved millions in misspent money. The authors of the Symplicity HTN-3 study state that the results emphasise "the importance of conducting blinded trials with sham controls in the evaluation of new medical devices before their clinical adoption".

The European regulatory bodies will have to question why they did not adopt the more cautious approach of the FDA in permitting use of the technique ahead of firm scientific evidence as to its benefit. More importantly perhaps, many patients – some 5,000 around the world, it is estimated – may now rightly ask if they might not have been spared from undergoing an ineffective procedure that was not without risk.

In this regard, the Symplicity HTN-3 paper states that "there were no significant differences in safety between the two groups", but even here there is a need for caution. The results on safety only extend to six months, and there is now evidence emerging from sensitive imaging techniques that the arterial damage induced by renal denervation may be substantial and lasting. There is certainly a need to evaluate any such consequences well beyond the six-month period and it is reassuring to know that the patients in the Symplicity HTN-3 will be followed for five years after randomisation.

The main lesson from this salutary tale of fiscal largesse attempting to overcome scientific reasoning is that there is no substitute for scientific evidence based on carefully conducted trials before any therapy – be it interventional or pharmacological – is recommended in clinical practice.

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